Therapeutic drug monitoring of daptomycin: a retrospective monocentric analysis

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Abstract: Background: Daptomycin dose is adjusted to body weight and renal function and is usually not guided by therapeutic drug monitoring (TDM). Daptomycin plasma concentration measurement was established at our institution in January 2009 and is now increasingly being used. The aim of this study was to describe and characterize variability in daptomycin exposure during routine clinical therapy. Methods: We collected daptomycin plasma concentrations that were measured at our institution during the period January 2009-July 2012. Additional clinical and demographic data and their association with daptomycin exposure was tested by a multilevel linear regression analysis. Results: A total of 332 daptomycin plasma concentrations were determined in 86 patients. 66% (n=218) of all determinations were trough concentrations (Cmin) and 34% (n=114) were peak concentrations (Cmax). Cmin ranged 2-68mg/L (median 16.7mg/L) and Cmax 20-236mg/L (median 66.2mg/L). A significant positive association of total dose, albumin, creatinine, and a significant negative association of dose interval and intermittent haemodialysis with Cmin was found in the regression analysis. Total dose and Intensive Care Unit (ICU)_$stay was significantly associated with Cmax (P < 0.05). However, only 28\% (P < 0.005) of Cmin variability and 8\% (P = 0.08) of Cmax variability was explained by the factors included in the analysis. Conclus$
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DOI: https://doi.org/10.1097/FTD.0000000000000196

Therapeutic Drug Monitoring of Daptomycin: a Retrospective Monocentric Analysis

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Disclosure:

Natascia Corti has participated in a Cubicin® advisory board for Novartis Switzerland twice in the past and was financially compensated. All other authors have not disclosed any potential conflicts of interest.

Keywords

Gram positive infection, antibiotic treatment, therapeutic drug monitoring

Short title: Retrospective Daptomycin TDM **Financial support**: none

Abstract

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Methods: We collected daptomycin plasma concentrations that were measured at our institution during the period January 2009-July 2012. Additional clinical and demographic data and their association with daptomycin exposure was tested by a multilevel linear regression analysis.

Results: A total of 332 daptomycin plasma concentrations were determined in 86 patients. 66% (n=218) of all determinations were trough concentrations (Cmin) and 34% (n=114) were peak concentrations (Cmax). Cmin ranged 2-68mg/L (median 16.7mg/L) and Cmax 20-236mg/L (median 66.2mg/L). A significant positive association of total dose, albumin, creatinine, and a significant negative association of dose interval and intermittent haemodialysis with Cmin was found in the regression analysis. Total dose and Intensive Care Unit (ICU)_-stay was significantly associated with Cmax ($P<0.05$). However, only 28% ($P<0.005$) of Cmin variability and 8% ($P=0.08$) of Cmax variability was explained by the factors included in the analysis.

Conclusion: Daptomycin plasma concentrations are often unpredictable as shown by highly variable drug exposure that is only partially explained by dose administered and underlying renal function.

Introduction

Therapeutic drug monitoring (TDM) is established for a number of anti-infective agents that are used in clinical care. Therapeutic plasma concentrations are defined based on clinical studies comparing plasma drug exposure to clinical efficacy and toxicity[1]. Although a toxicity threshold has been proposed for daptomycin induced CPK-elevation, no clinical trials exist that define optimal effective daptomycin plasma concentrations in different types of infection. Daptomycin (Cubicin®, Novartis, Basel, Switzerland) is a lipopeptide antibiotic active against Gram-positive organisms including methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant Enterococci ssp[2]. The actual labelled dose is 4mg/kg once daily for the treatment of complicated skin and soft tissue infections (cSSTI) and 6mg/kg for blood stream infections, including those with right-sided endocarditis caused by methicillin-resistant *S.aureus* and methicillin-susceptible strains[3]. Data that correlate daptomycin concentration and antimicrobial killing are derived from in vitro or animal studies where a concentration-dependent effect of daptomycin has been demonstrated, with area under the concentration curve (AUC)/minimal inhibitory concentration (MIC) ratio and peak concentrations (Cmax) /MIC ratio being the main determinants of bactericidal effect[4, 5].

Based on these findings, higher doses are recommended in severe and difficult to treat Gram-positive infections, such as bacteraemia, infective endocarditis and osteomyelitis[6], and in critically ill patients[7]. Daptomycin use and efficacy in different types of infection has mainly been investigated in retrospective studies[8, 9] where the focus was to investigate dosing regimen and outcome; daptomycin plasma concentrations were not determined in these studies. As daptomycin is mainly eliminated by the kidneys, prolongation of dosing interval from 24 hours (q24h) to 48 hours (q48h) is indicated in patients with a reduced glomerular filtration rate

(GFR) of <30mL/min with or without intermittent haemodialysis. Independent of the degree of renal impairment und type of renal replacement therapy used, high variability of daptomycin plasma concentrations can occur[10-12]. This is particularly the case in critically ill patients with Gram-positive sepsis, higher volume of distribution and increased daptomycin clearance has been observed with highly variable drug exposure leading to very low drug concentration in certain patients [7, 13, 14]. Therefore, TDM in these special populations might be warranted to optimize the dosing regimen and prevent either underdosing or excessive drug exposure associated with creatinine phosphokinase (CPK) elevation [15].

Daptomycin plasma concentration measurement at our institution was established in January 2009 and has now increasingly been used especially in the intensive care setting. The aim of this study was to investigate treatment indications in which daptomycin therapeutic drug monitoring was performed, to describe variability of daptomycin plasma concentrations and to determine the main factors associated with excessive or low drug exposure.

Material and Methods

In this retrospective chart review, we included all patients treated with daptomycin at the University Hospital in Zurich in the period January 2009 - July 2012 with at least one determination of daptomycin plasma concentration. The study was approved by the local Ethics Committee, Zurich, Switzerland. Samples were analysed by LC-MS/MS at the Institute of Clinical Chemistry as previously described[11]. The lower limit of quantification of the method was 0.03 mg/L, the precision 3.1% and the accuracy 101%.

We collected all available daptomycin plasma concentrations determined, clinical and demographic data, the corresponding dosage, dosing interval and renal function or type of renal replacement therapy at the time of measurement. Cmin was usually determined just before the next infusion and Cmax immediately after the end of infusion. Cubicin® was infused over 30minutes in all but one patient which received the infusion as a bolus over 2 minutes. In order

to characterize daptomycin dose as a function of body weight, total single administered dose recorded in the patient records was divided by body weight (kilogram).

Patients were divided in 4 Groups according to renal function and type of renal replacement applied: Group 1, creatinine clearance (CrCl) >30mL/min; Group 2, CrCl ≤30mL/min and no renal replacement therapy; Group 3, end stage renal disease with intermittent hemodialysis (IHD); Group 4, renal failure requiring continuous renal replacement therapy (CRRT). CRRT was performed either with Multifiltrate (Fresenius Medical Care, Homburg, Germany) using the capillary hemofilter AV 1000s (polysulfone, surface area 1.8 m^2) or with Prismaflex ST150 (Gambro AB, Lund, Sweden) using the capillary hemofilter AN69 ST (acrylonitril-sodium-methylsulfonate, surface area 1.5m^2). In 72 of 86 patients, CrCl was estimated by Cockcroft-Gault formula. In the remaining patients, the Modification of Diet in Renal Disease (MDRD) equation was used to estimate GFR. Analysis of variance (ANOVA) was applied to compare daptomycin plasma concentrations within the groups. Correlation of daptomycin dose and daptomycin plasma concentration were analysed within these groups by simple linear regression analysis using SPSS Version 22 (IBM Corp, Armonk, NY).

The independent association between daptomycin trough levels (Cmin), peak levels (Cmax) and the four renal function groups was investigated by multilevel linear regression analysis, taking into account repeated measurements in patients. The following covariates were included in the model to control for potential confounding: creatinine, dose interval, total administered dose (defined as total single dose administered on the sampling day), weight, gender, albumin plasma concentration and hospitalisation in a ICU. A separate analysis was additionally undertaken for dose normalized Cmax and Cmin (defined as Cmax or Cmin divided by total administered dose) at dose intervals of 24h or 48h. Total dose and dose interval were excluded as covariates for this analysis. Due to the skewed daptomycin trough and peak level distribution, regression analysis was performed on natural log (ln) transformed data. Residual

analysis was performed to check for the regression assumption. Analysis was performed with STATA Vers.12.1 (StataCorp LP, Texas).

Daptomycin trough levels and their respective CPK values were recorded and possible drug-induced CPK elevation was evaluated. CPK elevation was judged as possibly daptomycin related after exclusion of other causes (e.g. trauma or surgery) and the presence of a temporal relationship with daptomycin treatment. A toxicity threshold was defined as a daptomycin trough level of > 25mg/L based on the findings of Bhavnani et al., who reported an increased risk of CPK-elevation above a value of >24.3mg/L [15].

Results

Patient Characteristics

Patient characteristics and indication for daptomycin treatment are represented in Table 1. A total of 86 patients were included. Four patients were excluded because of incorrect sampling time points. Eighty percent of the patients studied were hospitalized, at least transiently, in the ICU. Four percent of daptomycin concentrations were determined on an outpatient basis. Daptomycin plasma concentrations were most frequently determined in *Enterococcus faecium* infections (44%) and in *coagulase negative Staphylococci* (CoNS) infections (28%). The following pathogens were isolated in 36 blood cultures: 19 *E.faecium*, 6 methicillin-resistant *Staphylococcus aureus* (MRSA), 6 CoNS and 1 *E.faecalis*, vanocomycin resistant *Enterococcus*, methicillin-susceptible *Staphylococcus aureus* (MSSA), *S.anginosus* and group B *Streptoccocus*. Additional antibiotics effective against the infecting pathogen were used in 46 patients (51%); 37 (41%) patients received daptomycin monotherapy. The remaining patients could not be evaluated either due to missing pathogen detection or unknown comedication.

Daptomycin dosing

152 The median daptomycin dose administered was 6mg/kg (range 2.7-13.8mg/kg) and the median
153 total dose was 500mg (150mg-1000mg). Data on daptomycin dosing interval in different renal
154 function groups are shown in Table 3. In 40 of 86 patients a high dose regimen (6mg/kg up to
155 13.8mg/kg) was administered.
156 In 10 patients, dose was adjusted based on daptomycin plasma concentration measurements.
157 However, this was done in an unsystematic way solely dependent on the decision of the treating
158 physician as no internal guidelines on target range were available. In 4 patients, the dose was
159 increased based on Cmin <2mg/L, 5.4mg/L and 14.9mg/L. In 5 patients, the daily dose was
160 decreased based on Cmin >50mg/L and 19.7mg/L and in one case based on a peak level of
161 133mg/L. In one patient, the reason for dose change was unclear.
162
163 Plasma concentrations
164 A total of 332 daptomycin plasma concentrations were determined. Sixty-six percent (n=218)
165 of all determinations were trough levels (Cmin) and thirty-four percent (n=114) were peak
166 levels (Cmax). In patients with multiple sampling, a median of 2 Cmin samples and 1 Cmax
167 sample were drawn per patient (range 0-14 and 0-15, respectively). Cmax was never
168 determined in patients with CrCl ≤30mL/min. Cmin ranged 2- 68mg/L (median 16.7mg/L) and
169 Cmax ranged 20-236mg/L (median 66.2mg/L). Time of first daptomycin measurement after the
170 first dose or after a dose change ranged 1-80 days (median 4 days) and 1-120 days (median 3
171 days) for Cmin and Cmax, respectively. In 77% of patients determination of first daptomycin
172 plasma concentration was performed after at least 3 days. When analyzed by renal function
173 groups, only in patients undergoing CRRT significant correlations were observed between
174 daptomycin dose (mg/kg) and Cmin (R^2 0.23, $p<0.05$) or Cmax (R^2 0.25, $p<0.05$). No
175 significant correlation with dose administered was found in the other groups.
176 The highest variability of daptomycin plasma concentrations was observed in patients with
177 CrCl ≤30mL/min and CrCl >30mL/min without renal replacement therapy (CV% 81% and

178 72% in CrCl ≤30 and CrCl >30mL/min versus CV% 69% and 63% in IHD and CRRT) (Figure
179 1a and 1b). Dose-normalized Cmin was more variable in patients with CrCl < 45mL/min than
180 in patients with moderately impaired or normal renal function or in patients undergoing renal
181 replacement therapy (Figure 2). In patients with CrCl ≤30mL/min and a dosing interval of
182 q48h, Cmin values were all below 20mg/mL whereas in those patients with a dosing interval of
183 q24h Cmin values higher than 20mg/mL were measured in 22% of the patients. Mean Cmin
184 values in the 48h and the 24h group were 15.7 ±16.9mg/L and 39.4 ±21.0mg/L, respectively.
185 This difference was statistically significant (student T-test $p<0.05$).
186 Cmin levels were significantly lower in patients with CRRT compared to patients without renal
187 replacement therapy independent of renal function (ANOVA $p<0.005$) (Figure 1a). Cmax was
188 slightly lower in CRRT patients compared to other renal function groups but this difference
189 was not statistically significant ($p=0.49$) (Figure 1b).
190 When patients with severely impaired renal function (CrCl ≤30mL/min, IHD, CRRT) were
191 compared to the CrCl >30mL/min group and controlled for creatinine level, dose interval, total
192 dose, weight, gender, albumin concentration, and ICU hospitalisation in the multilevel
193 regression analysis, patients with IHD were associated with lower Cmin ($p=0.041$), whereas
194 association in the CRRT group was not statistically significant ($p=0.227$) (Table 2a). In the
195 same analysis, a significant positive association of total daptomycin dose, albumin, creatinine,
196 and a significant negative association of dose interval with Cmin were observed. The multilevel
197 analysis determined total dose and ICU hospitalisation as factors significantly associated with
198 Cmax (Table 2b, $P<0.005$). In a separate analysis of dose normalized plasma concentrations,
199 Cmin/dose determined at 24h was negatively associated with dose interval, creatinine level and
200 positively associated with ICU-hospitalisation. For Cmin/dose determined at 48h, a significant
201 negative association of creatinine level, gender and albumin and a positive association with
202 weight, were observed. For Cmax/dose determined at 24h, only patients undergoing CRRT
203 were now associated with lower values compared with the CrCl>30mL/min group. No

significant association could be found for other covariates or clearance groups with Cmax/dose determined either at 24h or 48h. Overall, only 27% (adjusted R2 0.27, $p<0.005$), of Cmin variability and 8% (adjusted R2 0.08, P=0.08) of Cmax variability was explained by the covariates included into a multiple linear regression analysis. Residual analysis revealed no violation of the regression assumption.

Safety

Cmin values $\geq$ 25mg/L were found in 38% of patients with CrCl >30mL/min or CrCl $\leq$30mL/min, in 17% of IHD patients and in 7% of patients undergoing CRRT. Overall, 20 cases of mild CPK elevation were found of which only 4 were considered possibly related to daptomycin treatment. In these patients the highest CPK values ranged 201-346 U/L and maximum Cmin values were 9.6mg/L, 23.5mg/L, 50.1mg/L and 14.3mg/L, respectively. The last two patients were taking a statin concomitantly.

Discussion

In this retrospective survey we present daptomycin plasma concentrations derived from patients undergoing therapeutic drug monitoring whilst treated with daptomycin. Our data reflect the heterogeneity of a real-world hospital patient population in contrast to prospective pharmacokinetic studies published so far that report daptomycin plasma concentrations in defined patient populations under strict dosing regimens [7, 11, 14, 16, 17]. Accordingly, high variability in weight, comorbidities, treatment indications and dosing regimen was observed in our subjects and 60% had severely impaired renal function or were undergoing renal replacement therapy.

We found that Cmin and Cmax values were associated with total dose administered and Cmin was additionally positively associated with creatinine clearance and albumin level and negatively associated with dose interval. Even when the analysis was undertaken separately for

the two dosing intervals, 24h and 48h, and dose normalized Cmin and Cmax, creatinine clearance remained associated with Cmin/dose. However, the covariates investigated accounted for only 27% of Cmin variability and 8% of Cmax variability. Thus, more than 70% of the Cmin variability and more than 90% of the Cmax variability remains unexplained in our model. Renal function has been identified as the main factor associated with daptomycin clearance in population PK studies that investigated patients with different grades of renal impairment or severe Gram positive infection[14, 18]. Additional factors influencing daptomycin PK were a considerably larger volume of distribution compared to healthy volunteers in patients with acute bacterial infections[7, 13, 14] and in patients with severely impaired renal function[18]. In a subset of patients with MRSA bacteraemia, highly increased daptomycin clearance was observed with significantly lower daptomycin exposure despite a comparable dose administered in all patients[7]. However, a significant proportion of daptomycin clearance variability remained unexplained[14, 18]. In view of these findings, TDM may me considered an important tool for individualized daptomycin dosing[7].

Over one third of the subjects in our study were treated with a high dose regimen $\geq$6mg/kg. High dose daptomycin regimens of >6mg/kg have been recommended in complicated infections such as endocarditis, osteomyelitis and sepsis [6], whereas the maximum licensed dose is 6mg/kg for the treatment of *S.aureus* bacteraemia and right sided endocarditis. The variability of individual dosing in our patients within the high dose regimen might reflect the fact that 80% of indications were off label treatments such as enterococcal and *coagulase negative Staphyloccoci* infections, left-sided endocarditis, foreign body infection or osteomyelitis for which exact dosing recommendations have not been established due to the lack of prospective controlled studies. This might lead to a further prescribing variability among physicians.

Dosing intervals were not necessarily chosen according to product labelling, which recommends a prolongation of dosing interval to 48hours in patients with CrCl <30mL/min[3].

In particular, in severely impaired renal function (CrCl <30mL/min without renal replacement therapy), we noticed the highest heterogeneity of dosing interval (Table 3). In nearly half of these patients, the dosing interval was not adjusted to 48hours. This generated very high Cmin values far above 20mg/L, in contrast to the adjusted interval with Cmin below 20mg/L after 48hours. While correct dose use might reduce the risk for CPK-elevation, the 48h dose interval is still associated with significantly lower daptomycin exposure over 24h to 48h.

The impact of low daptomycin exposure during the second day in a 48h dose interval regimen upon efficacy and risk of development of resistance is still unclear. Few data exist on efficacy and safety of daily daptomycin administration in severe renal impairment. In a case series, daptomycin was administered daily at doses of 6-8mg/kg in three patients with severe renal impairment (GFR 10-30mL/min) over several weeks with an improved efficacy and no CPK elevation[19]. However, daptomycin plasma concentrations were not monitored. The authors recommend high dose regimen administered daily as initial therapy for patients with very severe infections and a GFR of 10-30mL/min.

A higher risk for CPK-elevation was associated with daptomycin trough concentrations of >24.3mg/L in a study by Bhavnani et al. [15] who analysed daptomycin plasma concentrations derived from a pivotal clinical study investigating daptomycin in the treatment of bacteraemia and endocarditis caused by *S.aureus*[20]. In our patients, 25% of all Cmin values were above 25mg/L. Concentrations as high as 68mg/L were tolerated without CPK elevation. This supports the fact that higher doses might be administered safely if needed for an efficient treatment.

Significantly lower daptomycin Cmin and Cmax concentrations were observed in critically ill patients undergoing CRRT, despite a high percentage of patients receiving daptomycin q24h. Daptomycin pharmacokinetics in CRRT have recently been investigated by several groups[11, 21-24] and a dosing interval q24h versus q48h has been discussed. The risk of under dosing on the second day after daptomycin administration in a q48h dosing regimen was also outweighed

against the risk of CPK elevation in q24h dosing. Our observational data here confirm our previously published prospective PK data in CRRT patients receiving 6mg/kg q24h [11] to ensure adequate daily drug exposure. As dose correlated significantly with daptomycin Cmin and Cmax values in CRRT patients, a high dose regimen q24h is probably necessary to ensure adequate daptomycin concentrations in critically ill patients who mostly suffer from severe infections. A study 8mg/kg q24h in CRRT is ongoing at our department.

Limitations of this study are due to the retrospective design. In some patients data collection was incomplete and the exact sampling time point after daptomycin administration could not be verified. Therefore, differences in duration of daptomycin infusion or incorrect sampling time could be an additional factor for Cmax and Cmin variability. We did not assess treatment outcome because less than half of our patients received daptomycin as monotherapy and the number of microbiologically evaluable patients was small. Additionally, our patient population was very heterogeneous concerning comorbidities and renal function and they also differed with regard to dose, duration of therapy and surgical interventions.

As we included only patients with daptomycin TDM performed, the population studied probably represents only a subset of the overall population treated with daptomycin at our institution. 50% of Cubicin® was in fact delivered to departments other than ICUs during the period of data collection, whereas 80% of our study patients were hospitalized in the ICU.

Conclusion

Our data demonstrate that, in an unselected patient population, daptomycin exposure is highly variable and is only partially explained by dose administered and underlying renal function. The factors accounting for most of the variability remains unclear and therefore daptomycin plasma concentrations are often unpredictable

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373

374 **Figure legends**

375 **Figure 1a and 1b** Daptomycin Cmin and Cmax values in different renal function groups

376 Legend

377 CrCl creatinine clearance, IHD intermittend hemodialysis, CRRT continuous renal
378 replacement therapy, Cmin trough concentrations, Cmax peak concentrations.

379

380

381 **Figure 2** Dose normalized Cmin values in different renal function groups

382 Legend

383 Cmin trough concentrations, CrCl creatinine clearance, CRRT continuous renal
384 replacement therapy, IHD intermittent hemodialysis. Filled circles represent q24h, triangles
385 q48h and quads a q12h dosing interval.

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